Claim 55. (New) The composition of claim 53, wherein the agent is covalently bound to the antisense oligonucleotide.--

Remarks

I. Claim Status

Claims 40-48, and new claims 53-55 are pending in the present application. Claims 49-52 have been withdrawn from consideration. Claim 40 has been amended in response to the double patenting rejection and rejections under 35 U.S.C. § 112, second paragraph. Support for the phrase "the sense strand" is found on page 35, lines 32-35 of the specification: "As used herein, the 'sense strand' of a nucleic acid contains the sequence that has sequence homology to that of mRNA. The 'anti-sense strand' contains a sequence that is complementary to that of the 'sense strand'. "

Support for the phrase "pharmaceutically acceptable excipient" is found in the Specification at page 57, lines 12-15. The description that follows on pages 57 and 58 support options for pharmaceutically acceptable excipients for delivery, including delivery of nucleic acids.

Support for new claims 53-55 is found in the Specification page 78, lines 32-36, which specifies that "the antisense oligonucleotide may also include molecules which carry agents (non-covalently attached or covalently bound) which cause the viral RNA to be inactive." No new matter is introduced by entry of the subject amendments.

II. The Restriction Requirement

The Examiner has divided the claims into three groups: Group I (claims 40-48), drawn to hepatitis C virus (HCV) antisense polynucleotides, class 536, subclass 24.5; Group II (claims 49-51), drawn to a delivery system for an HCV antisense polynucleotide and methods of treating a patient by administering an HCV antisense polynucleotide, class 514, subclass 44; Group III (claim 52), drawn to a method of inhibiting HCV viral replication, class 435, subclass 7.1.

In a conversation with the Examiner on December 9, 1997, applicants elected to prosecute the invention of Group I (claims 40-48) with traverse and now confirm that election. Applicants respectfully request reconsideration of the restriction between Groups I -

III on the grounds that a further search of those claims drawn to a delivery system for an HCV antisense polynucleotide comprising a liposome, methods of treating a patient by administering an HCV antisense polynucleotide, and a method of inhibiting HCV viral replication using an HCV antisense polynucleotide would not be burdensome in view of the search that must be conducted on the elected claims directed to the HCV antisense polynucleotides themselves. The additional search is not burdensome because using "HCV" and "antisense" and "polynucleotide" as search terms with the Boolean connecting term "and", would call up references for delivery systems and methods of Groups II and III. Thus, the search conducted by the Examiner for all three Groups together would not be burdensome.

Further, the claims of Groups I-III are not independent and distinct as required for restriction. The claims of Groups I-III are dependent subjects (and thus not independent) "as composition and the process for which the composition is used" as defined in MPEP 802.01. The disclosed relationship between the subject of Group I and the subjects of Groups II and III is that the claims of Group I disclose HCV antisense polynucleotides that can be used in the methods of delivery, methods of treatment, and methods of HCV viral inhibition of the claims in Groups II and III. The methods of Groups II and III are incapable of being performed without the compositions of Group I, and thus these inventions are not distinct from Group I under MPEP 802.01 which defines distinct as subjects that are capable of separate manufacture, use or sale. Practicing the methods of the claims of Groups II and III would always necessarily involve use of the compositions of the claims of Group I, and thus the subjects are not distinct. Thus, Groups I, II, and III are related and not distinct as defined in MPEP 802.01. Accordingly, reconsideration and withdrawal of the restriction between the claims of Group I - III is respectfully requested.

III. The Double Patenting Rejection Under 35 U.S.C. § 101

The Examiner has provisionally rejected claims 40-45 under 35 U.S.C. § 101 as claiming the same invention as that of claims 24-57 of copending allowed Application No. 08/040,564. On February 3, 1998, that application issued as U.S. Patent No. 5,714,596. Applicants have amended claim 40, from which claims 41-45 depend, to recite pharmaceutical compositions that also comprise a pharmaceutically acceptable exipient.

Thus, the claims of the issued patent '596 no longer fulfill the limits of claims 40-45 of the present application, and the chemical compositions are no longer the same. Accordingly, applicants request reconsideration and withdrawal of the double patenting rejection.

IV. The Rejection under 35 U.S.C. §112, Second Paragraph

Claims 40-48 were under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 40 has been amended to specify that the "antisense polynucleotide hybridizes to the sense strand of the genome of an HCV", and the phrase "or its complement" has been removed. Additionally, the language "and further comprises a pharmaceutically acceptable excipient" has been added to the claim, setting the claim apart from oligonucleotides used as probes, or PCR primers. As the amended claims are no longer vague or confusing, applicants request reconsideration and withdrawal of this rejection.

V. The Rejection under 35 U.S.C. §112, First Paragraph

Claims 40-48 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way so as to enable one skilled in the art to make or use the invention. Applicants submit that numerous sections of the specification guide one skilled in the art how to make and use the invention.

The primary guidance for the design of antisense polynucleotides is found in the specification at page 78, beginning at line 26:

> Antisense polynucleotide molecules are comprised of a complementary nucleotide sequence which allows them to hybridize specifically to designated rergions of genomes or RNAs. Antisense polynucleotides may include, for example, molecules that will block protein translation by binding to mRNA, or may be molecules which prevent replication of viral RNA by transcriptase. . . Antisense molecules which are to hybridize to HCV derived RNAs may be designed based upon the sequence information of the HCV cDNAs provided herein.

Thus, the specification teaches what portions of the genome antisense molecules should target.

Additionally, the specification states that "[t]he information obtained from further sequencing of the HCV genome(s), as well as from further characterization of the HCV antigens and characterization of the genome enables the design and synthesis of additional

probes and polypeptides and antibodies which may be used for diagnosis, for prevention, and for therapy of HCV induced NANBH, and for screening for infected blood and blood-related products." Page 40, line 32 through page 41, line 3.

Section II.H, beginning at page 61 of the specification, describes the design of diagnostic oligonucleotide probes and kits, which information applies equally to the design antisense oligonucleotides. The section teaches that "[t]he probes can be made completely complementary to the HCV genome. Therefore, usually high stringency conditions are desirable in order to prevent false positives. However, as shown infra, portions of the HCV genome are variable. Therefore, conditions of high stringency should only be used if the probes are complementary to regions of the viral genome which lack heterogeneity. The stringency of hybridization is determined by a number of factors during hybridization and during the washing procedure, including temperature, ionic strength, length of time, and concentration of formamide. These factors are outlined in, for example, Maniatis, T. (1982)." Page 62, lines 7-19.

Further guidance is contained in Section II.L of the specification, entitled "Screening for Anti-Viral Agents for HCV". which describes assays and screening techniques for testing antiviral agents apply to anti-viral agents, including "those which act with nucleic acids to prevent viral replication, for example, anti-sense polynucleotides, etc." Thus, applicants further provide methods for identifying, or determining whether one has identified, useful antisense polynucleotides.

Thus, one skilled in the art is enabled to make or use the invention by using the assays described in the Specification to select the antisense oligonucleotides most appropriate for use. Clearly those antisense polynucleotides that perform best in the assays or screening procedures would be preferentially selected by a practitioner. Applicants have clearly taught how to determine which portions of the genome are susceptible to antisense blockage. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Conclusion

In light of the foregoing amendments and remarks, it is believed that the application is in condition for allowance. Accordingly, reconsideration and favorable action on all claims

is earnestly solicited. If there are any questions concerning this communication, the Examiner is invited to call the undersigned at the telephone number provided below so that prompt disposition of this application can be achieved.

Respectfully submitted,

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